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TITLE: ATM Heterozygosity and the Development of Radiation-Induced Erectile Dysfunction and Urinary Morbidity Following Radiotherapy for Prostate Cancer

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**13. ABSTRACT (Maximum 200 Words)**

The goal of this training grant project is to determine whether the prevalence of *ATM* carriers among prostate cancer patients treated with radiotherapy that develop erectile dysfunction and urinary morbidity is greater than the prevalence of *ATM* heterozygosity among patients that do not develop this complication. Regardless of the scientific outcome of the proposal the PI will be left with a vast experience in translational research from which to form new hypotheses and research strategies as he begins his career as an independent physician scientist. To assure a well-rounded experience, the school of medicine will insure that the PI will participate for the first two years of the funded period in Mount Sinai's rigorous clinical research training program. The NIH sponsored program will give the PI formal instruction in Clinical Research and Policy Evaluation, Epidemiology and Biostatistics, Basic Science for the Clinical Investigator, Cultural, Illness, and Community Health Outcomes, Behavioral Medicine, and Ethical Issues in Clinical Research. Also the PI, while at Mount Sinai, will make significant progress in establishing collaborative relationships with well-established prostate cancer researchers and will continue this approach in order to expand the scope of the outlined proposal throughout the funding period of this grant.

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Introduction:

A significant proportion of prostate cancer patients treated with radiotherapy develop erectile dysfunction and urinary morbidity induced by exposure to a high dose of radiation. In some cases there are explanations for these reactions, such as doses to large volumes of normal tissue or pre-existing medical conditions such as diabetes or collagen vascular diseases. However, there exists an important subset of patients with no clear explanation for excessive post-treatment morbidity and the potential for a genetic basis must be considered. The purpose of this study is to investigate whether the ATM gene plays a role in this radiation sensitivity. This gene was selected, as the protein it encodes, plays a critical role in the response of cells to irradiation and the repair of radiation-induced damage. Furthermore, cells possessing one mutated copy of this gene are radiosensitive. In addition, the results of a pilot study screening breast cancer patients are supportive of the hypothesis that patients who are carriers of an ATM mutation are more likely to develop radiation-induced complications.

The principal goal of this project is to determine whether men who inherit a mutated copy of the ATM gene are more prone to the development of radiation-induced erectile dysfunction and urinary morbidity. This will be accomplished through comprehensive screening of the ATM gene for germline mutations. If a correlation is found between radiosensitivity and ATM heterozygosity, this would indicate that possession of a mutated copy of the ATM gene results in susceptibility to complications for prostate cancer radiotherapy patients. In addition, a determination will be made as to the pathogenic consequences of each ATM mutation through the use of functional studies that will examine the ability of the ATM protein to act normally in cells from patients who are carriers of a mutation in this gene. This project represents the first study to use the powerful DHPLC mutation screening technique to investigate the association between possession of a mutated ATM gene and both erectile dysfunction and the entire clinical course of a patient's urinary morbidity after treatment with radiation for prostate cancer. It is also the first study to examine whether there is a correlation between the presence of a mutation, development of a radiation-induced complication, and impairment of ATM protein function based upon cellular and molecular analyses.

Body:

I graduated from my residency in Radiation Oncology at Mount Sinai School of Medicine on 6/30/04. Therefore, my annual report covers the period from 7/1/04 to 1/31/05. I was accepted into the Mount Sinai Clinical Research Training Program, which is sponsored by an NIH K30 Clinical Research Curriculum Award. I have successfully completed the initial 6 months of the curriculum, which has included rigorous classes in Human Genetics, Basic Science for the Clinical Investigator, Epidemiology and Biostatistics and Ethical Issues in Clinical Research.

I have obtained consent to collect the medical information of 132 men treated with prostate brachytherapy since initiation of the study. I have prospectively collected details of their brachytherapy treatment, physical exam, and urinary, rectal and erectile functional scoring systems. In addition, for each man, I have collected and cryopreserved peripheral blood lymphocytes for the later steps in my training grant. Also, I have extracted the DNA of each man and also preserved this material for the later steps in my training grant. While carrying out these tasks I have also been working with my mentor, Barry Rosenstein, PhD, on his complimentary project which involves the characterization of the ATM gene in African -American female patients who developed breast cancer. This will be helpful in terms of carrying out the later aspects of my project because while doing this work I have learned how to construct optimal oligonucleotide sequences and carry out successful PCR reactions. I learned how to use the WAVE denaturing high performace liquid chromatography device and how to interpret DNA chromatograms of various exons.

I have begun to form collaborative research relationships with a number of investigators at the Mount Sinai Medical Center. Each week, I have been able to spend 4 hours with Simon Hall M.D., the chairman of Urology at Mount Sinai; we see patient's together at the Maury Dean Center for Prostate Health. From these meetings I have formed a number of research ties with his faculty. With Natan Bar-Chama MD, an expert in the diagnosis and treatment of erectile function, we are beginning a pilot project of MRI evaluation of the penile bulb in patient's who have developed radiation associated erectile function. With Micheal Diefenbach, PhD, a health psychologist in the Mount Sinai Urology department, I am serving as a consultant for an ongoing phase three randomized trial of behavior intervention prior to initiation of prostate cancer treatment. I have also established a working relationship with Andreas Beutler, M.D., a junior faculty in the Division of Medical Oncology and will be

serving as a consultant on a project involving creating a metastatic prostate cancer model in a mouse.

I have published two articles this year as primary author. (see appendix) In addition, I gave an oral presentation at this years American Society of Radiation Oncology meeting entitled, "ATM sequence variants are predictive of adverse radiotherapy response among patient's treated for prostate cancer." I also attended this years Gordon research conference on Radiation Oncology hosted by Elizabeth Travis, PhD and Simon Powell, M.D., PhD. I have also submitted a book chapter on Prostate Brachytherapy to Prostate Cancer Principles and Practice edited by Alan Partin et al. (see appendix) I will also be presenting an abstract at this years American Urological Association meeting in San Antonio, Texas entitled,"ATM sequence variants are predictive of the development of erectile dysfunction following radiotherapy for patient's treated for prostate cancer."

In terms of obtaining additional funding opportunities, I have applied to the NIH Loan Repayment Program and await their decision. In addition, in association with my mentor Barry Rosenstein, PhD, I have obtained funding as a co-investigator on a grant entitled, "ATM sequence variants are predictive of adverse radiotherapy response among African-American men" from the Veterans Administration Hospital in the Bronx, New York. I was awarded this year's ASTRO travel award in the amount of $1000. I have also been granted $300,000 from MedImmune Oncology, to serve as the principal investigator on a phase III randomized trial using Amifostine in the palliative setting for the treatment of metastatic disease. The protocol for this study is currently under development.

KEY RESEARCH ACCOMPLISHMENTS:

- Enlarged the Prostate Cancer database by 132 men.
- Obtained and preserved the lymphocytes of 132 men in preparation of experiments scheduled to begin in year two of the training program.
- Extracted, purified and quantified the DNA of 132 men in preparation for DHPLC.
- Have acquired a working knowledge of PCR and DHPLC through work on patient samples and experiments in progress in Dr. Rosenstein's laboratory.
- Have constructed a novel Iodine-125 based low dose irradiator to be used for radiosensitivity assays.
- I have constructed a radiosensitivity assay involving the used of histone H2Ax and low dose radiotherapy among previously characterized patient's with abnormalities in the ATM gene.

REPORTABLE OUTCOMES:

Publications:

Cesaretti JA, Stock RG, Lehrer S et al. ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer. Int J Radiat Oncol Biol Phys. 2005 Jan 1;61(1):196-202.

Cesaretti JA, Stone NN, Stock RG. Does prior transurethral resection of prostate compromise brachytherapy quality: a dosimetric analysis. Int J Radiat Oncol Biol Phys. 2004 Oct 1;60(2):648-53.

Stock RG, Cahlon O, Cesaretti JA et al. Combined modality treatment in the management of high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2004 Aug 1;59(5):1352-9.

Cesaretti JA, Stone NN, Kao J, Stock. Prostate Brachtherapy. In Prostate Cancer Principles and Practice. Editors: Kirby R, Partin A, Feneley M, Parsons JK Taylor & Francis Medical Books, Abingdon, England.

Presentations:

Cesaretti JA. "Real Time Brachytherapy: The American Experience." International Course on Brachytherapy, San Paolo Hospital, Febuary 2004, Savona, Italy.

Cesaretti JA. "Genetic Associations Are Predictive Of Adverse Outcomes Following Radiotherapy For Prostate Cancer." Radiological and Medical Physics Society of New York (RAMPS), Spring Symposium Advancing Radiation Oncology Planning Through an Understanding of Biology, May 2004, New York, New York.

Cesaretti JA. "Intensity Modulated Radiation Therapy for Brain Malignancies." IV Advanced Techniques and Technology in Image-Guided Brain and Spine Surgery, December 5, 2004, New York, New York.

Cesaretti JA, Stock RG, Atencio DA, Bernstein JL, Stone NN, Wallenstein S, Green S, Loeb KL, Kollmeier MA, Smith M, Rosenstein BS. "ATM Sequence Varients are Predictive of Adverse Radiotherapy Response Among Patients Treated for Prostate Cancer." ASTRO 46th Annual Meeting, October 2004, Atlanta, Georgia.

CONCLUSIONS:

My training grant is progressing on four important fronts. I am ahead of schedule in terms of patient accrual and acquisition of the necessary skills to complete the scientific phases of my project. After attending this year's Gordon Conference I have decided to include an assay of H2AX into my evaluation of the ATM functional status of patient's with adverse radiotherapy reactions. In addition, pending the results of my pilot study with Dr. Bar-Chama, I will be including imaging of the penile bulb into future comparative studies of functional outcomes following radiotherapy for prostate cancer.

I have begun to form a collaborative network intra and extra institutionally.

I have applied for an NIH loan repayment grant, and have obtained funding in association with my mentor to further expand my work on predictors of radiotherapy side effects.

I have completed one quarter of the coursework necessary to complete the K30 Physician Research Training Program; there are three more semesters of coursework are necessary to complete the program of study.

REFERENCES:

Cesaretti JA, Stock RG, Lehrer S et al. ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer. Int J Radiat Oncol Biol Phys. 2005 Jan 1;61(1):196-202.

Cesaretti JA, Stone NN, Stock RG. Does prior transurethral resection of prostate compromise brachytherapy quality: a dosimetric analysis. Int J Radiat Oncol Biol Phys. 2004 Oct 1;60(2):648-53.

APPENDICES:

Article - TURP Paper

Article - ATM Paper

Abstract - Prostate Cancer

Abstract - Prostate Cancer

Abstract - Breast Cancer

Abstract - Prostate Cancer

CV

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**PHYSICS CONTRIBUTION**

# DOES PRIOR TRANSURETHRAL RESECTION OF PROSTATE COMPROMISE BRACHYTHERAPY QUALITY: A DOSIMETRIC ANALYSIS

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**Purpose: To evaluate, in a retrospective review, prostate brachytherapy dosimetry outcomes relative to the transurethral resection of the prostate (TURP) cavity size to address the theoretical concern that an intraprostatic cavity may hinder adequate radioactive source placement.**

**Methods and Materials: A total of 73 patients who underwent prostate brachytherapy as part of their treatment of localized prostate cancer had a history of a prior TURP. Of these 73 patients, 37 underwent $^{125}$I implantation, 19 $^{103}$Pd implantation, and 17 partial $^{103}$Pd implantation. The dose was calculated using the dose to 90% of the prostate gland ($D_{90}$) from the 1-month post-implant dosimetric analysis. The doses were normalized relative to 100% of the prescription dose. Archived transrectal ultrasound images were used to determine the maximal length and width of the visible residual TURP cavities. The prolate spheroid or symmetric egg shape was used to calculate each residual cavity volume. The derived volume of the TURP cavity was divided by the measured ultrasound volume of the prostate at brachytherapy, creating a percentage of volume measurement for each prostate. All $p$ values, unless otherwise specified, were generated by comparing patients without a visible TURP defect with the subgroups of patients with a visible defect using the Student $t$ test.**

**Results: A visible residual TURP defect was noted on the operative transrectal ultrasound images of 55 (75%) of the 73 patients with a history of TURP before brachytherapy. The 18 patients without a visible TURP defect had a median $D_{90}$ of 96% and were used for subsequent statistical comparison. Thirty-six patients with a TURP defect <10% of the entire prostate volume had a median $D_{90}$ of 109% ($p = 0.02$). Thirteen patients with a TURP defect between 10% and 20% of the prostate volume had a median $D_{90}$ of 112% ($p = 0.03$). Six patients with a TURP defect >20% of the prostate volume had a $D_{90}$ of 89% ($p = 0.43$).**

**Conclusion: A visible residual TURP cavity that is assumed to have a prolate spheroid shape and occupy ≥10% of a prostate volume did not appear to be a statistically significant hindrance to proper dosimetric outcome.**


**Brachytherapy, TURP, Dosimetry, Prostate cancer.**

## INTRODUCTION

Permanent prostate brachytherapy has become a common treatment option for localized prostate cancer. Initially, patient selection was limited to those with smaller prostates and no history of transurethral resection of the prostate (TURP) (1). As more experience has been gained, the initial strict selection criteria have been liberalized. Patients with a history of benign prostatic hyperplasia who had required surgical relief of their obstructive symptoms had previously been excluded from seed implantation. TURP results in resection of tissue occupying the bladder neck and a substantial proportion of the central and transition zones (2, 3). From the brachytherapist's perspective, the TURP cavity may create a technical hurdle, because the remaining central tissue may not be adequate to permit proper seed placement and, by extension, a suboptimal dose distribution may result.

In addition to the TURP cavity possibly creating a problem with internal needle and seed placement, the resected prostate gland often becomes asymmetric and irregular, making straight alignment of needles and sources difficult to ensure a homogeneous dose that encompasses the entire gland. To address these concerns, we reviewed the preoperative ultrasound-based images of the prostate gland in all our patients who reported a history of TURP before implantation and correlated the TURP cavity size with the relevant dosimetric parameters.

## METHODS AND MATERIALS

Between January 1992 and December 2002, 73 consecutive patients with a history of prior TURP underwent implantation with the real-time technique and postoperative computed tomography (CT)-based dose evaluation.

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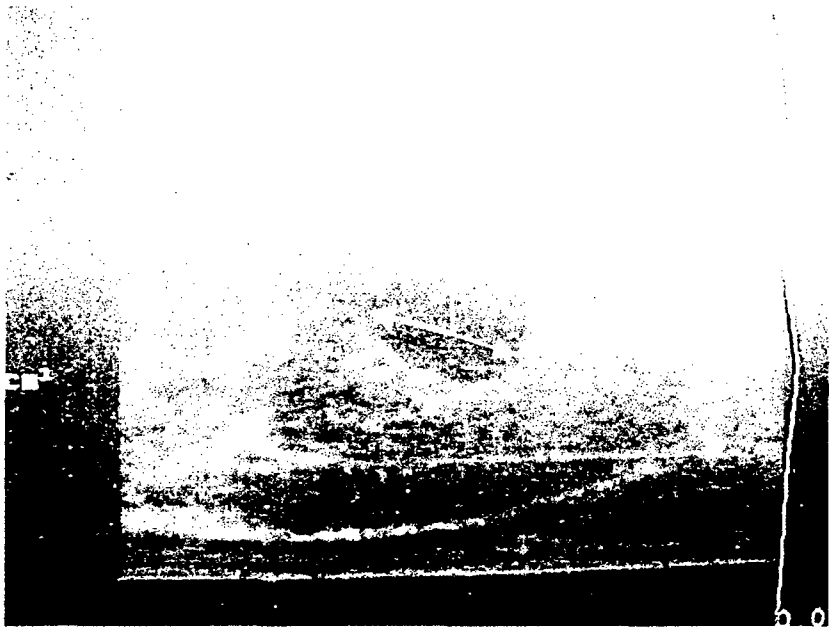

Fig. 1. Transrectal ultrasound image showing midline sagittal view of transurethral resection of the prostate cavity.

*Technique*

The implantation was performed using the previously described interactive ultrasound-directed technique (4, 5). The patient was placed in the extended dorsal lithotomy position, and a B&K model 8551 (1992–1995) or 8558 (1995 to present) biplanar ultrasound probe (B&K Medical, Wilmington, MA) was positioned in the rectum. A planimetry volume measurement with a 16F urethral catheter was performed using 5-mm transverse images of the prostate from the base to the apex. All transverse ultrasound images were printed and stored in the patient's chart. The volume was recorded, and the amount of activity to implant was determined by using an activity-per-volume table and, in later years, with an intraoperative computerized dosimetry system (Varian, Palo Alto, CA) (5, 6). The length of each prostate was determined from the mid-sagittal cut at the anterior, middle, and posterior aspects of the gland. The total number of seeds was determined by dividing the total activity indicated on a reference nomogram by the activity per seed to deliver a prescription dose of 160 Gy for $^{125}$I, 115 Gy (before NIST-99) and 124 Gy (after NIST-99) for full $^{103}$Pd and 90 Gy and 100 Gy, respectively, for partial $^{103}$Pd implantation. A partial implant with $^{103}$Pd uses a prescription dose of 100 Gy (American Brachytherapy Society recommendations), which is lower than the 124 Gy used for a full-dose implant. A partial implant implies that the dose from the implant is not the only dose delivered but is a component of the total dose (implant dose plus EBRT dose) (7). Generally, 75% of the total numbers of seeds required were implanted through the peripheral needles and 25% through the interior needles.

*Determination of TURP cavity size*

The ultrasound step-section images were reviewed to determine the size of the prostate TURP defect. A TURP defect was considered visible if it was >5 mm in diameter; this was necessary because all preimplant ultrasound measurements were done with a 16F urethral catheter, which has a diameter of approximately 5 mm. The catheter's position serves as a guide to intraoperative visualization and unavoidably alters the normal ultrasound image of the urethra as an arched-appearing closed slit (8). If the TURP defect was visible on transverse imaging, the midline sagittal and all additional transverse images were used to determine the maximal diameter and length using the ultrasound measurement grid and a ruler (Fig. 1). The residual cavity size was quantified by converting these two maximal measurements into a three-dimensional volume using the geometric formula for a prolate spheroid, $volume = (4/3)\pi hr^2$.

*Postimplant CT-based dosimetry*

Computed tomography-based dosimetry was performed 1 month after implantation with the ADAC Pinnacle system (ADAC Laboratories, Milpitas, CA) by taking 3-mm interval slices through the prostate volume. On every CT slice, the prostate, urethra, and rectum were contoured. All values were calculated with the American Association of Physicists in Medicine Task Group 43 (TG-43) formalism (9). Dose–volume histograms were generated of the prostate and urethra. For comparative analysis, the dose to 90% of the prostate gland ($D_{90}$) was converted to a percentage of the prescription dose, with 100% defined as the $D_{90}$ of 160 Gy for full $^{125}$I implantation, 124 Gy for full $^{103}$Pd implanta-

Table 1. Diameter, saggital length, and volume measurement of 55 TURP cavities visualized using ultrasound images

| Isotope | Patients ($n$) | Resected cavity diameter (cm) | Urethral cavity length (cm) | TURP cavity volume ($cm^3$) |
|---|---|---|---|---|
| Full $^{125}I$ | 30 | 1.1 (0.5–1.5) | 1.7 (0.5–4) | 2.6 (0.3–9.4) |
| Full $^{103}Pd$ | 15 | 1.3 (0.5–2.5) | 1.4 (0.5–2.5) | 3.4 (0.5–16.4) |
| Partial $^{103}Pd$ | 10 | 1 (0.8–1.2) | 2 (0.5–3) | 2.1 (0.3–4.5) |

*Abbreviation:* TURP = transurethral resection of prostate.
Data in parentheses are ranges.

tion, and 100 Gy for partial $^{103}Pd$ implantation. The changes instituted in the 1990s by issuance of the TG-43 and the NIST-99 recommendations were accounted for by normalizing the prescription doses to the prostate implants over time (9, 10).

*Statistical analysis*

The percentage of the volume of the TURP cavity relative to the entire measured volume of the prostate provided the basis of dosimetric analysis. The 73 patients were divided into four groups: 18 patients without a visible defect, 36 patients with a defect that was <10% of the entire volume of the prostate, 13 patients whose defect was between 10% and 20%, and 6 patients with a defect >20% of the prostate volume. In addition, a match-paired analysis was done comparing the $D_{90}$ values of the first 10 implants, without prior TURP (taken from a database of 1980 patients implanted between January 1992 and December 2002), yearly with the $D_{90}$ outcomes of the patients implanted with a prior history of TURP. All $p$ values, unless otherwise specified, were generated by comparing patients without a visible TURP defect with the subgroups of patients with a visible defect using the Student $t$ test.

## RESULTS

Of the 73 patients with a prior history of TURP, 37 were treated with a full $^{125}I$ implant, 19 with a full $^{103}Pd$ implant, and 17 with a partial $^{103}Pd$ implant. The mean prostate volume measured with planimetry before implant was 31.1 $cm^3$ (range, 8.4–85 $cm^3$); the mean prostate volume was 33.7 $cm^3$ (range, 8.8–89 $cm^3$) 1 month after implantation by CT-based dosimetry. The mean pretreatment ultrasound prostate volume was 33.1 $cm^3$ for $^{125}I$, 25.7 $cm^3$ for $^{103}Pd$, and 32.4 $cm^3$ for partial $^{103}Pd$. The mean $D_{90}$ for patients who were treated with $^{125}I$, $^{103}Pd$, and partial $^{103}Pd$ was 109% (95% CI, 104.3–113.7%), 98% (95% CI, 85.4–110.6%), and 104% (95% CI, 95–113%), respectively. The mean $D_{90}$ of all patients was 105% (95% CI, 100.6–109.5).

Of the 73 patients, 55 (75.3%) had a visible TURP defect. A defect was visible in 30 (81%) of the 37 patients who underwent $^{125}I$ implantation, 15 (79%) of the 19 patients treated with full $^{103}Pd$ implantation, and 10 (58.8%) of the 17 patients treated with partial $^{103}Pd$ implantation. The mean TURP defect diameter for all patients was 1.2 cm (range, 0.5–2.5 cm), and the mean urethral length defect was 1.7 cm (range, 0.5–4 cm; Table 1). The mean TURP volume for all implants was 2.7 $cm^3$ (range, 0.3–16.4 $^3$). The TURP cavity volume measurement was converted to a percentage of the measured prostate volume values, revealing a mean TURP cavity size for all visible defects of 10% (range, 1–68%) of the measured volume of the prostate. The mean TURP cavity volume was 8.3% for $^{125}I$, 14.6% for full $^{103}Pd$, and 8.2% for a partial $^{103}Pd$ implant. Overall, 24.7% had no defect, 49% had a defect of <10%, 17.8% had a defect between 10% and <20%, and 8.2% had a TURP defect >20% of the prostate size (Table 2).

Of the entire group of 73 patients, the 18 patients (24.7%) without a visible TURP defect had a median $D_{90}$ of 96% (range, 36–127%) of the prescription dose. Of the 73 patients, 36 (49%) had a TURP defect that was <10% of the entire prostate volume and had a median $D_{90}$ of 109% (range, 62–143%; $p = 0.02$). For the 13 patients (17.8%) with a TURP defect between 10% and <20% of the prostate volume, the median $D_{90}$ was 112% (range, 88–138%) of the prescription dose, significantly greater than for patients who did not have a visible TURP defect ($p = 0.03$). Six patients (8.2%) had a relatively large TURP defect of >20% of the prostate volume. Their

Table 2. Mean values of dosimetric parameters of patients divided by isotope

| Isotope | TURP volume as percentage of prostate volume | Ultrasound volume ($cm^3$) | Prescription dose (%) | $V_{150}$ (%) |
|---|---|---|---|---|
| Full $^{125}I$ | 8.3 | 2.6 | 109 | 59 |
| Full $^{103}Pd$ | 14.6 | 3.4 | 98 | 69 |
| Partial $^{103}Pd$ | 8.2 | 2.1 | 104 | 57 |

*Abbreviations:* TURP = transurethral resection of prostate; $V_{150}$ = volume of prostate receiving 150% of prescription dose.

Table 3. Dosimetric parameters of patients partitioned by TURP defect size

| TURP volume as percentage of prostate volume | Prescription dose (%) | $V_{150}$ (%) | $U_{30}$* | | |
|---|---|---|---|---|---|
| | | | $^{125}I$ | $^{103}Pd$ | Partial $^{103}Pd$ |
| None | 96 | 55 | 149 | 126 | 122 |
| <10 | 109 | 65 | 149 | 151 | 122 |
| 10–19 | 112 | 62 | 136 | 147 | 128 |
| ≥20 | 89 | 51 | 189 | 149 | 146 |

*Abbreviations:* $U_{30}$ = dose received by 30% of urethral volume; other abbreviations as in Table 2.
* All urethral doses are reported as percentage of the prescription dose.

median $D_{90}$ was 89% (range, 74–104%) of the prescription dose compared with the $D_{90}$ of 96% for patients without a visible TURP ($p = 0.43$; Table 3). No statistically significant relationship was found between the volume of the prostate receiving 150% of the prescription dose and the TURP size. In addition, because of the heterogeneity of the implant isotope and treatment strategy, it was not possible to compare meaningfully the urethral dose, as quantified by the greatest dose received by 30% of the urethral volume, among the patients with and without a TURP defect.

Of the 6 patients with a TURP defect of >20% of the prostate volume, 3 (50%) had a $D_{90}$ of <90% of the prescription dose in contrast to 4 (8%) of the 49 patients with a visible defect of <20% of the prostate volume ($p = 0.02$, Pearson's chi-square test). Of the 3 patients with a large TURP defect (>20%) and a $D_{90}$ of <90% of the prescription dose, 2 had undergone implantation in 1994. A matched-pair analysis of the $D_{90}$ outcomes of the first 10 patients implanted in 1994 revealed a mean $D_{90}$ of 78.9% in patients without a history of prior TURP vs. 90.2% in the 7 patients with a history of TURP ($p = 0.26$). Table 4 compares the yearly $D_{90}$ values of all patients with a history of prior TURP relative to the dosimetry outcomes of the first 10 patients implanted in each year from 1992 to 2002. The findings reveal that in each year no statistically significant difference resulted between the two treatment groups.

Eight patients with a history of multiple TURP procedures had a mean cavity volume of 3.7 $cm^3$ (95% CI 1.54–5.86) vs. 2.5 $cm^3$ (95% CI, 1.85–3.15) for patients with a single procedure ($p = 0.13$). In addition, patients who had undergone TURP <5 years before implantation had larger TURP cavities, with a mean of 3.3 $cm^3$ (95% CI, 2.14–4.45) vs. 1.6 $cm^3$ (95% CI, 1.25–1.95 $cm^3$, $p = 0.03$) if TURP had been performed >5 years before implantation.

Forty-five patients had undergone hormonal therapy for 6–9 months (3 months before implantation and 3–6 months after). The mean size of the hormone-treated prostates was 28 $cm^3$ (range, 8.5–77.5 $cm^3$) vs. 35.9 $cm^3$ (range, 9.2–85 $cm^3$) for the untreated ones ($p = 0.03$). No statistically significant difference was found in TURP cavity size as a percentage of the measured prostate volume between the hormone-treated patients (9.6%; 95% CI, 7.6–11.6%) and the untreated patients (10.6%; 95% CI, 5.6–15.6%; $p = 0.72$). In addition, the dosimetry results were similar for the two groups, with a mean $D_{90}$ of 107% (95% CI, 101–113%) of the prescription dose for the treated patients vs. 106% (95% CI, 97–115%) for the untreated patients ($p = 0.84$).

When evaluated according to prostate volume, 43 pa-

Table 4. $D_{90}$ as percentage of prescription dose for first 10 implants of each year from 1992 to 2002 vs. TURP patients implanted in that year

| Year | Mean $D_{90}$ (%) first 10 implants each year | History of TURP | | |
|---|---|---|---|---|
| | | Implants with history of TURP ($n$) | Mean $D_{90}$ (%) history of TURP | $p$ |
| 1992 | 58.4 | 1 | 35.9 | — |
| 1993 | 67.3 | 1 | 127.1 | — |
| 1994 | 78.9 | 7 | 90.2 | 0.26 |
| 1995 | 91.9 | 10 | 100.8 | 0.32 |
| 1996 | 94.2 | 11 | 111.3 | 0.06 |
| 1997 | 110.5 | 13 | 110.8 | 0.95 |
| 1998 | 110.1 | 3 | 109.9 | 0.99 |
| 1999 | 111.8 | 4 | 115.6 | 0.99 |
| 2000 | 113.6 | 1 | 102.8 | 0.99 |
| 2001 | 116.4 | 17 | 107.2 | 0.07 |
| 2002 | 109.3 | 5 | 114.5 | 0.41 |

*Abbreviations:* $D_{90}$ = dose to 90% of prostate gland; TURP = transurethral resection of prostate.

Table 5. Number of inner and outer seeds and needles partitioned by TURP cavity size

| TURP volume as percentage of prostate volume (%) | Inner seeds (*n*) | Outer seeds (*n*) | Inner/total seeds ratio (%) | *p* | Inner needles (*n*) | Outer needles (*n*) | Inner/total needles ratio (%) | *p* |
|---|---|---|---|---|---|---|---|---|
| None | 21 | 62 | 26 | — | 6 | 14 | 40 | — |
| ≤10 | 23 | 65 | 26 | 0.98 | 7 | 14 | 47 | 0.34 |
| 11 to ≤20 | 26 | 67 | 26 | 0.71 | 7 | 14 | 44 | 0.68 |
| >20 | 23 | 56 | 24 | 0.73 | 4 | 13 | 22 | 0.07 |

*Abbreviation:* TURP = transurethral resection of prostate.

tients had a preimplant volume of <30 $cm^3$ and 30 patients had a volume from 32 to 85 $cm^3$. Patients with a prostate volume of <30 $cm^3$ had a mean $D_{90}$ of 102% (95% CI, 96–108%), and patients with a volume of >30 $cm^3$ had a mean $D_{90}$ of 109% (95% CI, 102.6–115.4%, $p = 0.14$). In addition, patients with a prostate size >30 $cm^3$ had a mean TURP cavity volume of 3.3 $cm^3$ (95% CI, 1.8–4.8); smaller prostates were noted to have a mean TURP volume of 2.3 $cm^3$ (95% CI, 1.7–2.9, $p = 0.17$). A trend was noted toward larger relative TURP cavity sizes among prostates <30 $cm^3$, with a mean percentage volume of 12% (95% CI, 8–16%) compared with larger prostates with a relative TURP cavity size of 7% (95% CI, 4.5–9.5%, $p = 0.07$).

Table 5 outlines the comparison of the number of needles and seeds used in each implant by the relative size of the TURP cavity. By comparing the ratio of the number of inner needles and seeds used in each patient with the total number of needles and seeds used, one can test the influence of prostate TURP defect size on needle and seed placement while controlling for variations in prostate size. A trend was noted among patients with the largest TURP defect toward a more peripherally loaded implant. The ratio of inner to total needles placed was 22% (95% CI, 2–42%) for patients with a visible TURP; the difference in the ratio of inner to total needles used among patients without a visible TURP defect (40%, 95% CI, 30–50%) was not statistically significant ($p = 0.07$). No statistically significant associations were noted in the ratio of inner to outer seeds used in the implant.

## DISCUSSION

Prior TURP has historically been considered a relative contraindication for performing permanent seed brachytherapy (1). This concern arose from both the reported high complication rate in patients with a history of TURP and the technical difficulty in achieving adequate dose after TURP (11). Brachytherapy techniques that use a more peripheral approach to implantation have not been shown to be associated with increased morbidity in this setting (12).

This is the first study to examine the effect of prior TURP on the dosimetry outcome by examining the size of the TURP cavity. As demonstrated in this series, the TURP cavity is both visible and measurable by ultrasonography, revealing a relatively diverse anatomic variation among patients with a history of prior transurethral surgery. This variation did not appear to influence the quality of peripherally loaded implants in terms of the $D_{90}$, even though 26% of the patients were missing >10% of the central prostate volume. Also, no statistically significant influence was found on the volume of the prostate receiving 150% of the prescription dose; we were unable to directly compare the doses to 30% of the urethral volume because the variety in isotope and treatment strategies did not provide sufficient numbers for analysis.

We detected an influence on our implant technique of the largest TURP cavities, with a trend toward using relatively fewer centrally placed needles in those patients compared with in patients without an identifiable TURP defect. We believe the main reason for this was our emphasis on the interactive ultrasound-directed peripheral loading technique, which allows the central portion of the gland to remain free of very-high-dose regions. In addition, the real-time nature of our implants allows for intraoperative improvisation when such variations in expected anatomy as a significant TURP defect are identified. When reviewing the postimplant CT studies, the TURP defects were noted only among 18 (25%) of the 73 patients rather than the 55 (75%) detected by reviewing the ultrasound studies. The implication is that preplanning strategies reliant on CT volumetric studies may not be adequate to detect variations in the prostate's expected anatomy compared with the intraoperative ultrasound studies. Therefore, CT-based preplanning, although adequate for a large proportion of individuals with the expected anatomy, may fail to discern the subtleties in the anatomy of the central portion of the prostate (12).

Our series also offers some insight into the natural history of a TURP cavity. The patients who underwent TURP several years before implantation had smaller residual cavities than those who had undergone TURP more recently. The greater the interval between TURP and implantation, the more likely the prostate will grow and "fill in" this defect. This finding was dramatic in terms of the patient with the largest residual cavity of 68% of the TURP defect volume, in that his TURP had been approximately 2 months before the brachytherapy procedure. This observation may

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# *ATM* SEQUENCE VARIANTS ARE PREDICTIVE OF ADVERSE RADIOTHERAPY RESPONSE AMONG PATIENTS TREATED FOR PROSTATE CANCER

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**Purpose:** To examine whether the presence of sequence variants in the *ATM* (mutated in ataxia-telangiectasia) gene is predictive for the development of radiation-induced adverse responses resulting from $^{125}$I prostate brachytherapy for early-stage prostate cancer.

**Materials and Methods:** Thirty-seven patients with a minimum of 1-year follow-up who underwent $^{125}$I prostate brachytherapy of early-stage prostate cancer were screened for DNA sequence variations in all 62 coding exons of the *ATM* gene using denaturing high-performance liquid chromatography. The clinical course and postimplant dosimetry for each genetically characterized patient were obtained from a database of 2,020 patients implanted at Mount Sinai Hospital after 1990.

**Results:** Twenty-one *ATM* sequence alterations located within exons, or in short intronic regions flanking each exon, were found in 16 of the 37 patients screened. For this group, 10 of 16 (63%) exhibited at least one form of adverse response. In contrast, of the 21 patients who did not harbor an *ATM* sequence variation, only 3 of 21 (14%) manifested radiation-induced adverse responses ($p = 0.005$). Nine of the patients with sequence alterations specifically possessed missense mutations, which encode for amino acid substitutions and are therefore more likely to possess functional importance. For this group, 7 of 9 (78%) exhibited at least one form of adverse response. In contrast, of the 28 patients who did not have a missense alteration, only 6 of 28 (21%) manifested any form of adverse response to the radiotherapy ($p = 0.004$). Of the patients with missense variants, 5 of 9 (56%) exhibited late rectal bleeding vs. 1 of 28 (4%) without such alterations ($p = 0.002$). Of those patients who were at risk for developing erectile dysfunction, 5 of 8 (63%) patients with missense mutations developed prospectively evaluated erectile dysfunction as opposed to 2 of 20 (10%) without these sequence alterations ($p = 0.009$).

**Conclusions:** Possession of sequence variants in the *ATM* gene, particularly those that encode for an amino acid substitution, is predictive for the development of adverse radiotherapy responses among patients treated with $^{125}$I prostate brachytherapy. © 2005 Elsevier Inc.

ATM gene, Radiation sensitivity, DHPLC, Prostate cancer, Brachytherapy.

## INTRODUCTION

Ataxia-telangiectasia (A-T) is a rare autosomal recessive genetic syndrome caused by genetic mutations in both copies of the *ATM* gene (1). Generally, these mutations result in truncation of the encoded protein (2). A-T is characterized clinically by cerebellar degeneration, ocular telangiectasias, and immunodeficiency. Of particular interest has been the observation that radiotherapy patients with A-T experience devastating side effects after exposure to ionizing radiation (3), including severe skin necrosis and organ dysfunction. Understanding the function of the protein encoded by *ATM* advanced greatly after cloning of the *ATM* gene. Subsequent elucidation of the activity of the ATM protein revealed a central role orchestrating the cellular response to DNA double-strand breaks (4, 5). ATM-dependent modifications of the proteins encoded by the *p53*, *BRCA1*, *CHK2*, *NBS1*, *FANCD2*, *CDC25A*, and *RAD17* genes modulate cell cycle progression and DNA repair in response to environmental assaults and ionizing radiation (6–18).

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Table 1. Patient characteristics in addition to baseline urinary, rectal, and erectile function

| Characteristic | Number of patients (%) |
|---|---|
| Median age | 63 years (range: 48–78 years) |
| Coronary artery disease | 12 (32) |
| Angioplasty | 4 (11) |
| Hypertension | 6 (16) |
| Coronary bypass surgery | 3 (8) |
| Myocardial infarction | 2 (5) |
| Not otherwise specified | 1 (3) |
| Active smoker | 4 (11) |
| Reformed smoker | 9 (24) |
| Diabetes | 3 (8) |
| Pretreatment American Urologic Association urinary function score | |
| Good (0–7) | 28 (76) |
| Moderate (8–19) | 7 (19) |
| Severe (20–35) | 2 (5) |
| History of transurethral prostate resection before implant | 1 (3) |
| Preimplant ultrasound prostate volume | |
| ≤35 $cm^3$ | 8 (22) |
| 36–50 $cm^3$ | 20 (54) |
| >50 | 9 (24) |
| Erectile function | |
| 3 - Optimal | 22 (60) |
| 2 - Suboptimal but sufficient | 6 (16) |
| 1 - Insufficient | 5 (14) |
| 0 - None | 4 (11) |
| Ulcerative colitis/Crohn disease | 1 (3) |
| Hemorrhoids | 7 (19) |

Although the occurrence of alterations in both copies of the *ATM* gene is rare, individuals who are heterozygous carriers of a single *ATM* mutation may constitute more than 1% of the general population. It has been shown that cells derived from heterozygous individuals exhibit an intermediate degree of radiosensitivity between those of wild-type and homozygously mutated cells derived from people with A-T (19–21). Animal studies have found that heterozygous $ATM^{+/-}$ mice are more susceptible to radiation-induced cataracts compared with wild-type $ATM^{+/+}$ counterparts (22). These discoveries have led to the hypothesis that possession of one altered copy of the *ATM* gene may predispose patients receiving radiotherapy to adverse reactions associated with this treatment.

Several studies have screened the *ATM* gene in patients who displayed clinically abnormal radiosensitivity. Initially, the results of these studies were negative, primarily because the samples were analyzed using a test for protein truncation (23, 24). However, it is now recognized that the most prevalent *ATM* sequence alterations detected specifically in cancer patients are missense mutations causing amino acid substitution in the encoded protein (2). In view of this understanding, further studies were conducted using assays designed to detect this class of genetic alterations, and several positive findings correlating clinical radiosensitivity and *ATM* mutations have since been reported (21, 25, 26).

Table 2. Clinical tumor characteristics

| Characteristic | Number of patients (%) |
|---|---|
| PSA (ng/mL) | (range: 1.2–15, median: 6) |
| ≤4 | 3 (8) |
| >4–10 | 31 (84) |
| >10–20 | 3 (8) |
| Gleason score | |
| 5 | 5 (14) |
| 6 | 31 (84) |
| 7 | 1 (3) |
| Stage (AJCC 2002) | |
| T1c | 25 (68) |
| T2a | 8 (22) |
| T2b | 4 (11) |

One study, screening the *ATM* gene of 46 breast cancer patients treated with radiotherapy, revealed that 3 of 4 patients possessing an *ATM* missense mutation developed Grade 3–4 skin fibrosis. In contrast, none of the patients without a missense mutation developed this type of adverse radiotherapy response (26). Another study with a more limited genetic analysis of the *ATM* gene in which only 8 specific variants were genotyped reported that 4 of 6 breast cancer patients homozygous for the G→A transition polymorphism at nucleotide 5557, which transforms an aspartic acid into an asparagine at position 1853 of the protein, exhibited clinically abnormal radiosensitivity (25). In addition, it was reported that a patient discovered to be heterozygous for insertion of a guanine at position 3637, resulting in a frame-shift leading to a stop codon (TAG) at nucleotide 3681, experienced severe skin and subcutaneous tissue effects after conventional radiation therapy in the adjuvant setting for breast cancer (21). Cells from this patient displayed a radiosensitivity between the values for normal cells and those from patients with AT. Finally, Hall *et al.* reported that 3 of 17 prostate cancer patients exhibiting radiation-related morbidity after radiotherapy possessed *ATM* mutations (27).

The purpose of this study was to examine the hypothesis that the presence of *ATM* sequence alterations is predictive for the development of adverse radiotherapy responses among prostate cancer patients. We have screened the expressed portions of *ATM* and short adjacent intronic regions that may encompass putative splice sites for DNA sequence variations (28). This work was accomplished using denaturing high-performance liquid chromatography (DHPLC) with DNA samples derived from lymphocytes obtained from an unselected group of 37 men treated with low-dose-rate $^{125}I$ brachytherapy for prostate cancer. We explore any potential association of acute and late erectile, rectal, and urinary functional outcomes with *ATM* alterations using standard morbidity measuring tools.

## METHODS AND MATERIALS

### *Patients*

Peripheral blood lymphocytes were collected from a consecutive series of 37 patients seen for periodic evaluation who under-

Table 3. The postimplant dosimetric parameters of all patients

| Implant characteristics | Median (range) |
|---|---|
| Total activity (mCi) | 42 (27.3–62.6) |
| Needle number | 24 (16–29) |
| Seed number | 103 (70–171) |
| Dose to 90% of the prostate (Gy) | 196 (156–220) |
| Dose to 100% of the prostate (Gy) | 111 (78–139) |
| Volume of prostate receiving 150% of prescription dose (%) | 68 (36–84.3) |
| Dose to 30% of the urethra (Gy) | 228 (23–265) |
| Amount of rectum receiving 100% prescription dose ($cm^3$) | 0.7 (0.01–3.56) |

went $^{125}I$ prostate brachytherapy for early-stage prostate cancer between June 1997 and April 2002. All patients had biopsy-proven adenocarcinoma with central pathology review performed on all specimens. Patients were staged according to American Joint Cancer Commission standard (29). Patient and tumor characteristics are outlined in Tables 1 and 2. Brachytherapy was administered via the transperineal approach using a transrectal ultrasound probe to direct the placement of each radioactive source within the prostate (30). The implant characteristics are enumerated in Table 3. The prescription dose for all implants was 160 Gy corrected for TG-43 recommendations (31). Patients returned at approximately 4 weeks after the implant for detailed CT-based dosimetric analysis. In this study, a comprehensive dose–volume histogram analysis was available for the bladder, rectum, urethra, and prostate of each patient. Patient follow-up included digital rectal examinations and serial PSA measurements. Biochemical failure was defined using the American Society for Therapeutic Radiation and Oncology consensus definition (32).

### *Definition of adverse response*

Patient clinical data were available from the departmental prostate cancer tissue repository database, which prospectively collected data for the 2,020 patients who underwent prostate brachytherapy at Mount Sinai between June 1990 and February 2004. All patients underwent a detailed history and physical examination before implantation followed by a directed history and physical examination at 6-month-interval follow-up evaluations. Acute and late rectal toxicities were graded using the Radiation Therapy Oncology Group (RTOG) morbidity criteria (33). Patients who developed either RTOG grade level 1 or 2 rectal effects were classified as having an adverse response. Urinary tract morbidity was prospectively measured using the American Urologic Association Symptom Score (AUASS) sheet that was administered before the implant and at each follow-up evaluation (34). The urinary quality of life score from the AUASS was used for analysis with a score of 6 or "terrible" long-term urinary quality of life classified as an adverse response. Erectile function was assessed using the following scoring system: 0, complete inability to have erections; 1, able to have erections but insufficient for intercourse; 2, can have erections sufficient for intercourse but considered suboptimal; and 3, normal erectile function. The derivation and relevance of this scoring system have been previously described (35, 36). For this analysis, a decline by 2 points was considered a significant prospective decline in erection function, and these patients were classified as having an adverse response. In addition, beginning in June 2000, the validated International Index of Erectile Function (IIEF-5) was used as a complementary method to better quantify late erectile dysfunction (ED) (37). A score of 0–2 was judged as an adverse response. The last completed form was used for this study, because the relatively recent development of the IIEF-5 did not allow for a prospective evaluation in most patients.

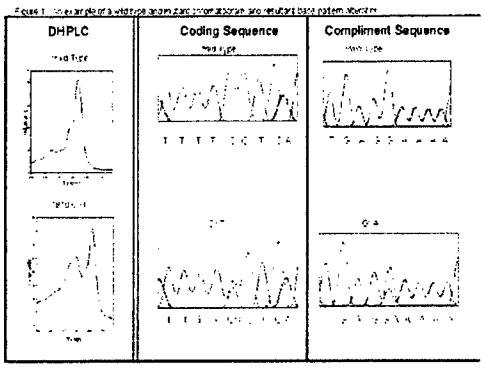


Fig. 1. An example of a wild-type and mutant chromatogram and resultant base pattern alteration.

The goals of the project were discussed with each patient as outlined by the guidelines approved in the institutional review board protocol, and written informed consent was obtained.

### ATM *exon characterization*

DNA isolation from lymphocytes was accomplished using Ficoll separation as described previously (38). Polymerase chain reaction (PCR) was used to amplify each of the 62 exons, and short intronic regions flanking each exon, that comprise the coding region of the *ATM* gene using primers previously described (39). DHPLC analysis was performed on a WAVE Nucleic Acid Fragment Analysis System (Transgenomic, Omaha, NE) using buffer gradient and temperature conditions calculated using WAVEmaker software (version 3.3; Transgenomic) designed for this purpose. An example of a wild-type and mutant chromatogram and resultant base pattern alteration is seen in Fig. 1. Exons with an aberrant DHPLC chromatogram underwent DNA forward and reverse sequencing using an ABI PRISM 377 DNA Sequencer (Foster City, CA).

### *Statistical analysis*

Analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL) software. Differences in proportions were derived using the Fisher's exact *t*-test. A two-sided $p$ value of $\leq 0.05$ was considered to indicate statistical significance.

## RESULTS

A total of 21 *ATM* sequence variants, representing 17 different alterations, were detected in expressed portions of the gene, or within 10 nucleotides of each exon encompassing potential splice sites, in 16 of the 37 patients screened (Table 4). It should be noted that most of the sequence variants detected in this group of patients represent genetic

Table 4. Each patient with toxicity, genetic, comorbid, and follow-up data

| Patient (#) | *ATM* alteration | Prospective erectile decline | Last follow-up IIEF-5 | Rectal bleeding | Urinary quality of life | $D_{90}$‡ (Gy) | Comorbidities | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 4473C>T, 149.1F>F | No | 24 | No | 1 | 184 | CAD | 21 |
| 2 | | No | 18 | No | 4 | 192 | | 36 |
| 3 | 4578C>T, 1526P>P; 5557G>A, 1853D>N | Yes | 2 | RTOG 1 | 6 | 180 | | 67 |
| 4 | | No | 20 | No | 3 | 208 | Tob | 37 |
| 5 | | No | 16 | No | 2 | 205 | Tob | 29 |
| 6 | | No | 24 | No | 1 | 165 | | 36 |
| 7 | | * | 10 | No | 0 | 191 | | 70 |
| 8 | | No | † | No | 2 | 220 | | 49 |
| 9 | 1810C>T, 604P>S | Yes | 16 | No | 6 | 208 | | 19 |
| 10 | 378T>A, 126D>E; IVS7-8insT; 1176C>G, 392G>G | Yes | 1 | No | 2 | 197 | DM | 12 |
| 11 | 2685A>G, 895L>L; 2614C>T, 872P>S | Yes | 1 | RTOG 1 | 1 | 205 | | 40 |
| 12 | IVS38-8T > C | No | 24 | No | 1 | 159 | | 60 |
| 13 | | * | 23 | No | 2 | 174 | DM, CAD | 31 |
| 14 | | No | 1 | No | 3 | 210 | CAD | 20 |
| 15 | IVS38-8T>C | No | 19 | No | 4 | 164 | Tob | 39 |
| 16 | | No | 14 | No | 0 | 183 | | 59 |
| 17 | | * | 5 | No | 0 | 169 | | 44 |
| 18 | | No | 22 | No | 2 | 220 | | 40 |
| 19 | | No | 12 | No | 2 | 206 | | 26 |
| 20 | | * | 21 | No | 2 | 199 | Tob | 37 |
| 21 | | * | 2 | No | 2 | 174 | DM, CAD | 25 |
| 22 | 198A>C, 66K>K | * | 1 | No | 1 | 217 | | 40 |
| 23 | | No | 23 | No | 1 | 160 | | 25 |
| 24 | | Yes | 9 | No | 2 | 184 | | 39 |
| 25 | | * | 6 | No | 4 | 218 | | 32 |
| 26 | 4388T>G, 1463F>C; 1810C>T, 604P>S | * | 2 | RTOG 2 | 2 | 209 | CAD | 13 |
| 27 | | No | 15 | No | 4 | 205 | | 32 |
| 28 | 5071A>C, 1691S>R | Yes | 1 | RTOG 2 | 2 | 192 | | 45 |
| 29 | 3161C>G, 1054P>R | No | 19 | No | 2 | 197 | | 27 |
| 30 | IVS62+8A>C | No | 19 | RTOG 1 | 0 | 217 | CAD | 47 |
| 31 | 4578C>T, 1526P>P | Yes | 8 | No | 0 | 193 | | 26 |
| 32 | 2038T>C, 680F>L | No | 19 | RTOG 1 | 0 | 219 | | 31 |
| 33 | | No | 24 | No | 2 | 162 | | 71 |
| 34 | | * | 3 | No | 0 | 168 | CAD | 69 |
| 35 | 5557G>A, 1853D>N | No | 20 | No | 0 | 186 | | 58 |
| 36 | | No | 18 | No | 1 | 197 | | 43 |
| 37 | IVS22-6T>G | No | 22 | No | 3 | 210 | | 29 |

*Abbreviations:* CAD = coronary artery disease; DM = diabetes mellitus; RTOG = Radiation Therapy Oncology Group; Tob = active smoker.

* Patient had a suboptimal erectile function before implant.

† Patient did not fill out IIEF-5.

‡ Dose to 90% of the prostate gland via brachytherapy.

alterations that have been previously reported as polymorphisms in *ATM* (40–42). For this group, 10 of 16 (63%) exhibited at least one form of adverse radiotherapy response. In contrast, of the 21 patients who did not harbor an *ATM* sequence variation, only 3 of 21 (14%) manifested any form of adverse response ($p = 0.005$). There were 9 patients found carrying missense mutations encoding for amino acid substitutions in the *ATM* protein. Missense mutations represent sequence alterations that are more likely to impact functional integrity. Of the 9 patients with missense mutations, 7 (78%) exhibited at least one form of adverse response. In contrast, of the 28 patients who did not have a missense mutation, only 6 of 28 (21%) manifested any form of adverse response to the radiotherapy ($p = 0.004$). Moreover, 5 of 9 (56%) patients with missense mutations exhibited an adverse response in two or three of the three organ systems evaluated (Patients 3, 9, 11, 26, and 28), whereas none of the remaining 28 patients without such sequence changes exhibited morbidity in more than one evaluated organ system ($p = 0.003$).

RTOG Grade 1 or 2 rectal bleeding was seen in 5 of 9 (56%) patients with missense mutations vs. 1 of 28 (4%) of

Table 5. Univariate analysis of variables that may predict for urinary, erectile, and rectal morbidity. All $p$ values derived from 2-sided Fisher's exact $t$-test

| Variable | Two radiation morbidities | SHIM erectile decline | Prospective erectile decline | Rectal Bleeding RTOG 1,2 | Urinary quality of life "terrible" |
|---|---|---|---|---|---|
| Dose ≥210 Gy | 1 | 0.34 | 0.29 | 0.14 | 1 |
| Diabetes | 1 | 0.12 | 0.25 | 1 | 1 |
| Smoking | 1 | 0.56 | 0.55 | 1 | 1 |
| Coronary artery disease | 1 | 0.17 | 0.55 | 0.32 | 1 |
| *ATM* alteration | 0.0003 | 0.01 | 0.009 | 0.002 | 0.05 |

*Abbreviations:* RTOG = Radiation Therapy Oncology Group; SHIM = Sexual Health Inventory for Men.

those without these genetic alterations ($p$ = 0.002). The median amount of rectal tissue exposed to the prescription dose of 160 Gy among the individuals with rectal bleeding was 0.87 $cm^3$ (range, 0.04–1.24), which is below previously published rectal dosing parameters for prostate brachytherapy and predicts a low probability of late radiation-induced proctitis based upon dose alone (43).

Severe ED as quantified by IIEF-5 occurred in 5 of 9 (56%) patients with missense mutations compared with 3 of 27 (12%) of patients without these sequence abnormalities ($p$ = 0.01). When considering only patients with sufficient erectile function before radiotherapy prospectively, a significant correlation was also noted between the development of erectile dysfunction in men with missense mutations, 5 of 8 (63%), as opposed to 2 of 20 (10%) in men without these types of variants ($p$ = 0.009). In addition, both patients who reported a "terrible" urinary quality of life had *ATM* missense alterations (2 of 9, 22%) vs. 0 of 28 patients without missense alterations ($p$ = 0.05).

The effects of total dose, diabetes, coronary artery disease, and active tobacco use were analyzed separately in relation to each of the adverse responses defined. No independent variable achieved statistical significance (Table 5), other than the presence of an *ATM* sequence alteration. In addition, none of the patients experienced a palpable local or biochemical disease recurrence.

## DISCUSSION

Sixty-three percent (10 of 16) of prostate cancer patients treated with $^{125}I$ brachytherapy who were found to be carriers of sequence variants either within the exons or in short intronic regions flanking exons of the *ATM* gene developed at least one form of urinary, sexual, or rectal adverse response. In contrast, only 14% (3 of 21) of patients without *ATM* sequence variations displayed some form of adverse response. Furthermore, when only those patients specifically harboring missense mutations are considered, 78% of these patients developed adverse responses compared with 21% who did not possess these types of sequence abnormalities. The results of this study are supportive of the hypothesis that genetic alterations in the *ATM* gene are predictive for the development of adverse responses resulting from radiotherapy.

Radiation-induced permanent sexual dysfunction has a substantial negative impact on the quality of life of men treated for prostate cancer. Brachytherapy series have reported a widely variable incidence of reduced sexual potency after implantation (35, 36, 44–48), ranging from 14% to 50%. In this unselected series, 30% (11 of 37) of patients overall had erectile dysfunction, a figure that is consistent with previous reports. Of even greater significance, however, is that 63% of patients in this study with good preirradiation erectile function developed prospectively evaluated ED if they possessed an *ATM* missense mutation vs. 10% of men without such an alteration. The correlation of ED with *ATM* missense mutations was also apparent when men were evaluated only at last follow-up with the validated IIEF-5. Using this evaluation tool, it was found that 56% of patients with missense mutations, vs. 12% without these genetic changes, developed severe ED. These findings attest to the predictive power of *ATM* mutational status for ED and warrant validation of this striking correlation in a larger group of individuals.

A second significant correlation observed in this study is that of postradiation rectal bleeding with *ATM* sequence alterations. All of the patients who experienced late rectal bleeding had *ATM* sequence alterations. The 2 patients who manifested comparatively severe rectal bleeding, RTOG Grade 2, had DNA missense mutations. In particular, the patient with the most serious rectal bleeding was a carrier of two nonconservative missense mutations and displayed this morbidity at only 5 months after radioactive seed implantation, rather than the more typical 1.5 to 2 years. This patient underwent colonoscopy and biopsy, which identified distal proctitis and an absence of the classic telangiectasias. Patients who undergo brachytherapy receive relatively low rectal doses compared with the use of external beam irradiation involving a larger pelvic field. Most radiation-related rectal bleeding secondary to prostate cancer radiotherapy is self-limited and innocuous, but there are patients who are inordinately affected and develop rectourethral fistulas (49, 50). In these instances, it could prove even more

important to predict which patients may be radiosensitive.

With respect to the correlation of urinary symptoms with *ATM* abnormalities, the 2 patients reporting a late "terrible" urinary quality of life at last follow-up both had nonconservative missense mutations. The spectrum of affected organs for these patients included a severe decline in prospectively measured erectile function. In addition, 1 of the 2 patients had rectal bleeding. The AUASS form appears effective in quantifying the most severe urinary morbidity, but there is a relatively long symptomatic period after the implant that may decrease this instrument's power to discern differences in intermediate-term urinary function.

It may be anticipated that the tumors possessed by patients harboring ATM mutations could also be radiosensitive and that these men may exhibit higher levels of tumor control compared with patients not harboring sequence alterations. However, the patients included in this study had low-risk prostate cancer, and all were treated with optimal implants based upon evaluation of their postbrachytherapy dosimetric studies (51). It is therefore not surprising that none of the patients screened in this study failed treatment. As reported previously by our institution, these patients have an expected freedom from PSA failure of 94% at 8 years (52). Therefore, it was not possible to examine whether *ATM* genetic status conferred tumor radiosensitivity.

Clearly, there is a strong association between sequence variants in the *ATM* gene and increased clinical radiosensitivity. Nevertheless, it is highly probable that *ATM* is not the only gene whose alteration can predispose patients to adverse radiotherapy responses. Thus, the patients in this series who exhibited pronounced radiation-related morbidity, but proved negative for *ATM* sequence variants, may possess alterations in other genes associated with radiation response. Among the additional radiosensitivity candidate genes that have now been linked with enhanced radiation effects are *TGFβ1*, *XRCC1*, *XRCC3*, *SOD2*, and *hHR21* (53–56). Alterations in these genes are also likely to serve as important potential predictors of adverse radiotherapy response. In view of the clinical associations observed between radiation sensitivity and the *ATM* gene in this study, combined with the reported association of other genes, it is critical that comprehensive genetic screening of radiotherapy patients for DNA sequence variations in candidate genes associated with radiation response be accomplished, because the results of such studies could yield significant patient benefit.

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**ABSTRACT FINAL ID:** 2191;

**TITLE:**
Hormonal Therapy Reduces the Risk of Post-Implant Urinary Retention in Symptomatic Prostate Cancer Patients with Glands Larger Than 50 cc

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**INSTITUTIONS (ALL):** 1. Radiation Oncology, Mount Sinai School of Medicine, New York, NY, USA. 2. Urology, Mount Sinai School of Medicine, New York, NY, USA.

**ABSTRACT BODY:**

**Purpose/Objective:** Controversy exists regarding the optimal management of men with prostate glands > 50 cc who undergo permanent seed implantation. Previous studies have suggested that pre-treatment with hormonal therapy (HT) may actually increase the risk of urinary retention or urinary symptoms when compared to patients not receiving HT. Unfortunately, no prior studies have analyzed the influence of urinary symptoms prior to the initiation of HT. In this study we compare a cohort of men with prostate glands > 50 cc treated by implant alone to a similar cohort also treated with pre-implant HT in whom the pre-HT data was available for analysis.

**Materials/Methods:** 404 patients with Gleason score < 7, PSA < 10, T1c-T2b prostate cancer were treated with implant alone (n=176) or with 3 months of HT (n=228) prior to implant. 338 (84%) received I-125 and 66 Pd-103. Prostate volumes (PV) and international prostate symptom scores (IPSS) were determined prior to initiation of HT and just before implantation. IPSS were collected at 3, 6 and every 6 months post implant. Urinary retention (UR) was designated if a patient required reinsertion of a urinary catheter post-implant. PSA failure was determined by ASTRO definition. The effects of hormonal therapy on prostate size, urinary retention and IPSS scores were tested by Chi-Square method. Survival (PSA) was calculated by Kaplan Meier method.

**Results:** Mean follow-up was 36 months (range 1-139). Mean pre-treatment gland size was 74 cc (range 50-151) in the group that received HT and 60.3 cc (range 50-117) in the group that did not ($p=0.037$). In the HT group, PV decreased to a mean of 48.6 cc (mean reduction 35%, $p<0.001$) prior to implantation. UR occurred in 11.4% in those treated with HT vs 11.9% without HT ($p=0.84$). UR risk did not increase with increasing PV. The mean maximum post implant IPSS score was 16.7 without HT vs 15.6 with HT ($p=0.261$). In patients with initial IPSS > 15, UR occurred in 4/12 (33.3%) of those not receiving HT vs 0/27 in the HT group ($p=0.002$, RR 4.4, 95% CI 2.1-8.1). 24 month mean IPSS remained elevated (10.4 vs 5.9 pre-implant, $p<0.001$) for those without HT, while it returned to baseline in the HT patients (8.2 vs 9.7, $p=0.06$). Urinary QOL also remained elevated in the non HT patients (1.3 vs 2.3, $p<0.001$) compared to the HT group (1.2 vs 1.7, $p=0.195$). 6-year PSA failure free rates were similar for each group (93%).

**Conclusions:** The data from this study confirms the benefit of using pre-implant HT in patients with PV > 50 cc. HT mostly benefits the subgroup of patients who present with symptomatic prostatism and an IPSS > 15. Minor benefit was also noted in 24 month IPSS and QOL scores in the HT group. PSA freedom from failure was no different in the two groups, confirming the lack of benefit for HT in improving disease control in low risk patients.

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**ABSTRACT FINAL ID:** 89.

**TITLE:**
Does Local Control Impact Prostate Cancer Specific Survival (PCSS) Within the First 10 Years Following Brachytherapy

**AUTHORS (ALL):** Stock, Richard Glenn[1]; Stone, Nelson Neal[2, 1]; Cesaretti, Jamie Allan[1]

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2. Urology, Mount Sinai School of Medicine, New York, NY, USA

**ABSTRACT BODY:**

**Purpose/Objective:** In theory, local failure following prostate cancer therapy can lead to metastases and eventual death from the disease. Treatment and disease related factors which contribute to local control should, in turn, affect prostate cancer specific survival (PCSS). PCSS was analyzed in relationship to pre-treatment and treatment parameters as well as to other outcome endpoints to shed light on the relationship of local control and death from prostate cancer within 10 years following prostate brachytherapy.

**Materials/Methods:** 1,510 patients with t1 to t3 prostate cancer and median age of 66 years (range: 39 - 88) were treated with permanent seed implantation from 1990 to 2002. They were followed from 1 to 13 years (median - 6). Pre-treatment parameters were as follows: PSA (range: 0.3 - 300, median - 7.35), stage ( $\leq$ t2a in 65%, $\geq$t2b in 35%), score ( $\leq$ 6 in 69%, 7 in 21% and 8-10 in 10%). Patients were treated with implant alone (I-125 or Pd-103) in 41%, hormonal therapy and implant in 27%, and implant and external beam (+ - hormonal therapy) in 32%. BED calculations were performed using an alpha/beta ratio of 2 based on the D90 and external beam doses to enable various isotopes and treatment approaches to be compared. For example, a D90 of 140Gy for I-125 = BED of 147, a D90 of 100Gy (NIST '99) for Pd-103 BED of 133, 45Gy of external beam = BED of 63. PSA failure was calculated using the ASTRO definition. 2 years post-treatment prostate biopsies (6 cores) were recommended for all patients.

**Results:** The actuarial freedom from PSA failure, PCSS and overall survival at 10 years were 76%, 91% and 67%. 403 patients underwent post-treatment biopsies at 2 years and 15% were positive. Of the pretreatment factors, Gleason score had the most significant effect on PCSS. PCSS at 10 years was 93% for score $\leq$ 6, 85% for 7 and 86% for 8-10 ($p<0.0001$). PCSS at 10 years was 90% for PSA $\leq$ 10, 88% for >10-20, and 91% for >20 ($p = 0.28$). PCSS at 10 yrs was 99% for stage $\leq$t2a and 85% for stage $\geq$t2b ($p = 0.007$). Low, moderate and high risk patients had 10 year PCSS rates of 99%, 87% and 90%, respectively ($p = 0.0006$). Treatment approach did not significantly affect PCSS ($p = 0.13$). In the 130 pts who experienced a PSA failure, the 10 yr PCSS was 76% compared to 99% for those without failure ($p<0.0001$). PSA doubling time in those patients with a PSA failure had a profound effect on PCSS. In univariate analysis, doubling time cut-points of 3, 6 and 12 months all significantly affected PCSS (all p values < 0.0001). Actuarial 10 year PCSS for patients with doubling times $\leq$ 3 mos, $\leq$ 6 months and $\leq$ 12 months were 0%, 30% and 61%, respectively. Although dose (using a BED cut-point of 150) had a significant effect on PSA failure ($p = 0.0001$), it had no effect on PCSS with rates of 97% and 95% for doses $\leq$ 150 and > 150, respectively ($p = 0.9$). Although biopsy results significantly correlated with PSA failure ($p< 0.0001$), they did not significantly affect PCSS. Patients with negative biopsies had a PCSS of 98% versus 83% for patients with a positive biopsy ($p = 0.3$).

**Conclusions:** The above data suggest that although factors which are closely related to local control such as dose and biopsy outcomes significantly correlate with PSA failure, they do not impact 10 year PCSS rates. This, along with the strong correlation of PSA doubling times and Gleason score with PCSS suggest that many patients dying of prostate cancer within 10 years of therapy probably have microscopic disseminated disease at diagnosis. Longer follow-up will be needed to determine if those with local failure and low BED values will eventually succumb to the disease.

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**ABSTRACT FINAL ID:** 131;

**TITLE:**
*ATM* Sequence Variants and Adverse Radiotherapy Response in Breast Cancer Patients

**AUTHORS (ALL):** Rosenstein, Barry S.[1,2]; Andreassen, C. N.[3]; Alsner, J.[3]; Overgaard, M.[3]; Cesaretti, J. A.[1]; Atencio, D. A.[1]; Green, S.[1]; Formenti, S. C.[2]; Stock, R. G.[1]; Overgaard, J.[3].

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3. Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

**ABSTRACT BODY:**

**Purpose/Objective:** To examine the hypothesis that women who are carriers of genetic alterations in the *ATM* gene are more likely to develop subcutaneous fibrosis following radiotherapy for treatment of breast cancer compared with patients who do not possess DNA sequence variations in this gene.

**Materials/Methods:** DNA samples isolated from fibroblast cell lines that were established from 41 women treated with radiotherapy for breast cancer were screened for genetic alterations in the *ATM* gene using denaturing high performance liquid chromatography (DHPLC). This is a high throughput assay that provides a high level of accuracy and sensitivity for the detection of nucleotide substitutions as well as short deletions and additions. These patients were all treated with post-mastectomy radiotherapy in Aarhus, Demark from 1978-1982 using a three-field technique using two fractionation protocols. Thirty-four patients received 12 fractions to a minimum target dose of 36.6 Gy specified at the level of the mid-axilla or to an irradiated dose of 51.4 Gy irrespective of AP diameter. The other 7 patients were given a minimum target dose of 40.9 Gy in 22 fractions also specified at the mid-axilla. Each patient was evaluated for subcutaneous fibrosis in each individual treatment field. The absorbed dose for each field was converted to a biological 2 Gy equivalent dose. Dose response curves were determined using logit analysis and the dose that resulted in a 50% incidence of grade 3 fibrosis ($ED_{50}$) estimated (for details see Radiother. Oncol. 69:127-35, 2003).

**Results:** A total of 28 genetic alterations in the expressed portions of the *ATM* gene, or within 10 bases of each exon in regions encompassing putative splice sites, were detected in 22 patients. Because of the relatively large fraction sizes used for treatment of the majority of these patients, the biological doses were often relatively high and therefore grade 3 level fibrosis was noted in 37% of the individual treatment fields examined. The $ED_{50}$ (95% confidence of interval) of 60.2 (55.7-65.1) Gy calculated for patients without a sequence variation did not differ significantly from the $ED_{50}$ of 58.4 (54.0-63.1) Gy for the group of patients with any *ATM* sequence abnormality. However, the $ED_{50}$ was estimated at only 53.7 (50.2-57.5) Gy for those patients who were either homozygous or heterozygous for the G>A transition polymorphism at nucleotide 5557 which results in substitution of asparagine for aspartic acid at position 1853 of the ATM protein. This was substantially lower than the $ED_{50}$ of 60.8 (57.0-64.8) Gy for patients not carriers of this sequence alteration. Most notably, the enhancement ratio of 1.13 (1.05-1.22), representing the ratio of the $ED_{50}$ values, was significantly greater than unity and supports the conclusion that the *ATM* codon 1853 Asn/Asp and Asn/Asn genotypes are associated with radiosensitivity. It was not possible to detect any significant changes in the $ED_{50}$ for women with other sequence variants as the number of patients with any specific alteration, other than possession of the minor adenine allele at nucleotide 5557, was too low to reach statistical significance.

**Conclusions:** This study suggests that possession of the *ATM* nucleotide 5557 G>A missense polymorphism is predictive for the development of grade 3 fibrosis in breast cancer patients treated with radiotherapy.

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(No Table Selected)

(No Image Selected)

**ABSTRACT FINAL ID:** 1117;

**TITLE:**
ATM Sequence Variants are Predictive of Adverse Radiotherapy Response Amond Patients Treated for Prostate Cancer

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**ABSTRACT BODY:**

**Purpose/Objective:** To examine whether the presence of sequence variants in the ATM (mutated in ataxia telangiectasia) gene is predictive for the development of radiation-induced adverse responses resulting from 125I prostate brachytherapy for early stage prostate cancer.

**Materials/Methods:** 37 patients, with a minimum of one year follow-up, who underwent 125I prostate brachytherapy of early stage prostate cancer were screened for DNA sequence variations in all 62 coding exons of the ATM gene using denaturing high performance liquid chromatography (DHPLC). The clinical course and post-implant dosimetry for each genetically characterized patient was obtained from a database of 2020 patients implanted at Mount Sinai Hospital since 1990.

**Results:** 21 ATM sequence alterations located within exons, or in short intronic regions flanking each exon, were found in 16 of the 37 patients screened. For this group, 10/16 (63%) exhibited at least one form of adverse response. In contrast, of the 21 patients who did not harbor an ATM sequence variation, only 3/21 (14%) manifested radiation-induced adverse responses ($p=0.005$). Nine of the patients with sequence alterations specifically possessed missense mutations, which encode for amino acid substitutions, and are therefore more likely to possess functional importance. For this group, 7/9 (78%) exhibited at least one form of adverse response. In contrast, of the 28 patients who did not have a missense alteration, only 6/28 (21%) manifested any form of adverse response to the radiotherapy ($p=0.004$). 5/9 (56%) of patients with missense variants exhibited late rectal bleeding versus 1/28 (4%) without such alterations ($p=0.002$). Of those patients who were at risk for developing erectile dysfunction, 5/8 (63%) patients with missense mutations developed prospectively evaluated erectile dysfunction (ED) as opposed to 2/20 (10%) without these sequence alterations ($p=0.009$).

**Conclusions:** Possession of sequence variants, in the ATM gene, particularly those which encode for an amino acid substitution, is predictive for the development of adverse radiotherapy responses among patients treated with 125I prostate brachytherapy.

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## EDUCATION

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| 2004 – present | Assistant Professor<br>Department of Radiation Oncology<br>Mount Sinai School of Medicine, New York, New York<br>▪ Member MSSM CME Advisory Board |
| 2000 - 2004 | Resident Physician<br>Department of Radiation Oncology<br>Mount Sinai School of Medicine, New York, New York<br>▪ Chief Resident 2003 – 2004 |
| 1999 - 2000 | Internship<br>Department of Internal Medicine<br>St. Luke's - Roosevelt Hospital, New York, New York |
| 1995 - 1999 | M.D.<br>School of Medicine<br>State University of New York at Stony Brook, Stony Brook, New York<br>▪ President, History of Medicine Club |
| 1993 - 1995 | Post-baccalaureate Pre-med Program<br>School of General Studies<br>Columbia University, New York, New York |
| 1989 - 1993 | B.A., History<br>Columbia College<br>Columbia University, New York, New York<br>▪ John Jacob Astor Scholar, 1989 - 1993<br>▪ Co-founder, Columbia Hiking Club<br>▪ Leader, Columbia Outdoor Orientation Program |

## RESEARCH EXPERIENCE

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| 1993 - 1995 | Research Assistant<br>Department of Pathology, College of Physicians & Surgeons<br>Columbia University, New York, New York<br>▪ Lab focus on study of neuronal cytoskeleton and plaque-associated disease states. |

## GRANTS

Basic Science Travel Grant
ASTRO Research Evaluation Committee
ASTRO's 46th Annual Meeting in Atlanta, GA from October 3-7, 2004

Physician Research Training Award, PCO31163, 2003,
Prostate Cancer Research Program.
Sponsor: Department of Defense.
Principle Investigator: **Cesaretti JA**
Mentors: Stock RG, Rosenstein BA
Project entitled, "ATM Heterozygosity and the Development of Radiation-Induced Erectile Dysfunction and Urinary Morbidity Following Radiotherapy for Prostate Cancer."
Total award, $700,000 over 5 years.

Phase III randomized prospective trial
Sponsor: MedImmune Oncology
Principle Investigator: **Cesaretti JA**
Project entitled,"In the setting of palliative radiotherapy, does radioprotection with Amifostine improve an individual's quality of life?"
Total award, $300,000 over 1 year

## PUBLICATIONS

**Cesaretti JA**, Stone NN, Stock RG. "Urinary symptom flare following I-125 prostate brachytherapy." *Int J Radiat Oncol Biol Phys* 2003 Jul 15; 56(4):1085-92.

Stock RG, Stone NN, **Cesaretti JA**. "Prostate-specific antigen bounce after prostate seed implantation for localized prostate cancer: descriptions and implications." *Int J Radiat Oncol Biol Phys* 2003 Jun 1; 56(2):448-53.

Stock RG, Cahlon O, **Cesaretti JA**, Kollmeier MA, Stone NN. "Combined Modality Treatment in the Management of High Risk Prostate Cancer." *Int J Radiat Oncol Biol Phys* 2004 Aug 1; 59(5):1352-1359.

**Cesaretti JA**, Stone NN, Stock RG. "Does a prior transurethral resection of the prostate compromise brachytherapy quality: a dosimetric analysis." *Int J Radiat Oncol Biol Phys.* 2004 Oct 1; 60(2):648-653.

**Cesaretti JA,** Stock RG, Atencio DA, Bernstein J, Stone NN, Wallenstein S, Green S, Loeb KL, Kollmeier MA, Smith M, Rosenstein BS. "ATM sequence variants are predictive of adverse radiotherapy response among patients treated for prostate cancer." In Press, *Int J Radiat Oncol Biol Phys.*

**Cesaretti JA,** Stock RG, Stone NN. "Brachytherapy." Submitted Book Chapter, Prostate Cancer: Principles and Practice, Ed by Kirby R, Partin AW, Feneley M, Parsons JK. Taylor and Francis Medical Books.

Dosoretz AM, Stock RG, **Cesaretti JA**, Stone NN. "Role of external beam radiation and hormonal therapy in low, intermediate and high risk patients treated with permanent radioactive seed implantation." Submitted, *Brachytherapy.*

Kollmeier MA, Stock RG, **Cesaretti JA**, Stone NN. "Urinary Morbidity Following Post-brachytherapy Transurethral Resection of the Prostate." In Press, *Jnl of Urol.*

## ABSTRACTS

**Cesaretti JA**, Atencio DA, Stock RG, Stone NN, Green S, Bernstein JL, Wallenstein S, Loeb K, Chalon O, Kollmeier MA, Smith MJ, Rosenstein BA. "*ATM* Mutational Status is Associated with an Increased Severity and Earlier Onset of Radiation-Related Rectal Morbidity Among Patients Treated with $^{125}$I Prostate Brachytherapy." *Proceedings of the Radiological Society of North America* 2003 Nov.

**Cesaretti JA**, Stone NN,Stock RG. "Late exacerbation of urinary symptoms following I-125 prostate brachytherapy." *Int J Radiat Oncol Biol Phys* 2002 Oct 1; 54(2) Supl 1:45.

**Cesaretti JA**, Stock RG, Stone NN, Kollmeier M. "A TURP defect does not compromise prostate implant dosimetry." *Brachytherapy* 2003 May 1; 2(1): 66.

Dosoretz AM, Stock RG, **Cesaretti JA**, Stone NN. "Role of external beam radiation therapy in low, intermediate, and high risk patients treated with permanent radioactive seed implantation." *Int. J Radiat Oncol Biol Phys* 2003 Oct 1; 57(2) supl 1:171.

Loeb KL, Stone NN, **Cesaretti JA**, Stock RG. "The effect of intra-operative computer based dosimetry on urinary symptom severity." *Brachytherapy* 2003 May 1; 2(1): 65.

**Loeb KL,** Cesaretti JA, **Stock RG, Stone NN. "TURP cavity size is associated with urinary symptom severity following I-125 prostate brachytherapy."** ***Proceedings of the Radiological Society of North America*** **2003 Nov.**

Kollmeier MA, Stone NN, **Cesaretti JA**, Stock RG. "Comparison of Race and Prostate Cancer Outcome in Patients Treated with Brachytherapy." *Brachytherapy* 2004 May 1; 3(1): 290.

## PRESENTATIONS

**Cesaretti JA**, Stone NN, Stock RG. "Late Exacerbation of Urinary Symptoms Following I-125 Prostate Brachytherapy." ASTRO 44th Annual Meeting, October 2002, New Orleans, Louisiana.

**Cesaretti JA**, Atencio DA, Stock RG, Stone NN, Green S, Bernstein JL, Wallenstein S, Loeb K, Chalon O, Kollmeier MA, Smith MJ, Rosenstein BA. "*ATM* Mutational Status is Associated with an Increased Severity and Earlier Onset of Radiation-Related Rectal Morbidity Among Patients Treated with $^{125}$I Prostate Brachytherapy." RSNA 89th Annual Meeting, November 2003, New York, New York.

**Cesaretti JA**. "Interactive Ultrasound Guided Prostate Brachytherapy; The Mount Sinai Experience." First Annual Radiation Oncology Symposium, Galliera Hospital, November 2003, Genoa, Italy.

**Cesaretti JA**. "Real Time Brachytherapy: The American Experience." International Course on Brachytherapy, San Paolo Hospital, Febuary 2004, Savona, Italy.

**Cesaretti JA**. "Genetic Associations Are Predictive Of Adverse Outcomes Following Radiotherapy

For Prostate Cancer." Radiological and Medical Physics Society of New York (RAMPS), Spring Symposium Advancing Radiation Oncology Planning Through an Understanding of Biology, May 2004, New York, New York.

**Cesaretti JA.** "Intensity Modulated Radiation Therapy for Brain Malignancies." IV Advanced Techniques and Technology in Image-Guided Brain and Spine Surgery, December 5, 2004, New York, New York.

## POSTER DISCUSSION

**Cesaretti JA**, Stock RG, Atencio DA, Bernstein JL, Stone NN, Wallenstein S, Green S, Loeb KL, Kollmeier MA, Smith M, Rosenstein BS. "ATM Sequence Varients are Predictive of Adverse Radiotherapy Response Among Patients Treated for Prostate Cancer." ASTRO 46th Annual Meeting, October 2004, Atlanta, Georgia.

## POSTERS

**Cesaretti JA**, Stock RG, Stone NN, Kollmeier M. "A TURP defect does not compromise prostate implant dosimetry." American Brachytherapy Society, 24th Annual Meeting, May 2003, New York, New York.

**Cesaretti JA**, Stock RG, Rosenstein BS. "Education and training in the six general competencies in a radiation oncology residency program." ACGME Annual Conference, March 2003, Chicago, Illinois.

Kollmeier MA, Stone NN, **Cesaretti JA**, Stock RG. "Comparison of Race and Prostate Cancer Outcome in Patients Treated with Brachytherapy." American Brachytherapy Society, 25th Annual Meeting, May 2004, Barcelona, Spain.